



Review

DNA condensation induced by metal complexes



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ABSTRACT

DNA is stored in a highly compact, condensed phase in viruses, bacteria and eukaryotes. $\text{Co}(\text{NH}_3)_6^{3+}$ is a well-known inorganic cation that can induce DNA condensation, and numerous $\text{Co}(\text{III})$, $\text{Co}(\text{II})$, $\text{Fe}(\text{II})$, $\text{Ca}(\text{II})$, $\text{Cu}(\text{II})$, $\text{Ni}(\text{II})$, $\text{Zn}(\text{II})$, $\text{Ru}(\text{II})$, $\text{Pt}(\text{II})$ and $\text{La}(\text{III})$ complexes have been evaluated as DNA condensing agents. In this review, we divided these metal complexes into four distinct classes based on the mechanism of DNA condensation: (i) complexes with high positive charges that condense DNA via electrostatic interaction, (ii) complexes with planar intercalative ligands that condense DNA via π - π interaction, (iii) complexes that bind with DNA through hydrogen bonds, and (iv) complexes that covalently bind to DNA. Some applications of these metal complex-based DNA condensing agents in gene vectors and antitumor agents are also presented.

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1. Introduction

DNA is a very long and strongly charged heteropolymer. In vivo, DNA must fit into the very small space of a virus capsid, bacteria nucleoid or the nuclear region in eukaryotic cells, while the length

of a stretched single DNA molecule may be up to a several dozen centimetres long, depending on the organism. Thus, DNA chains must collapse into compact and highly ordered particles containing only one or a few molecules (DNA condensation) [1]. Usually, several DNA molecules are incorporated into the condensed structure, and therefore, it is difficult to distinguish between condensation and aggregation. The term condensation is generally used when the aggregate is of finite size and has an orderly morphology. DNA condensation acts as a barrier to radiation-induced DNA damage [2]

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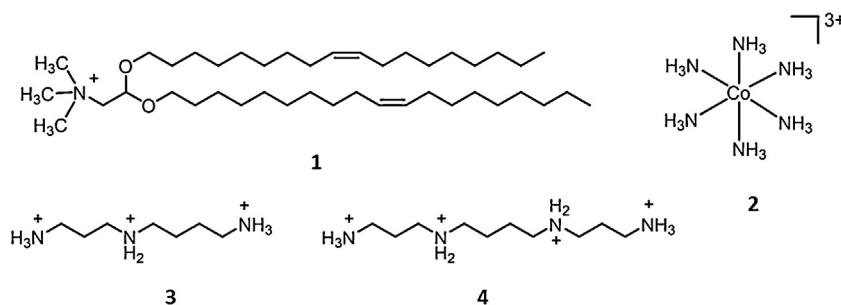


Fig. 1. Chemical structures of the commercial lipid agent DOTMA (1), hexaminecobalt(III) (2), spermidine³⁺ (3) and spermine⁴⁺ (4).

and oxidative damage [3]. The radioprotective/oxiprotective effect can likely be explained by the tight DNA packing prohibiting the access of regulatory molecules to DNA; in addition, the DNA repair process is accelerated in the condensed DNA, which has a high density. The condensation of free DNA *in vitro* has long been of interest as a potential model for DNA packing *in vivo* and in gene therapies, providing a promising means of non-viral gene delivery.

Many compounds have been studied for compacting DNA, such as the polycations spermidine³⁺ and spermine⁴⁺ [4–6], inorganic cations [5,7,8], lipids [9,10], polymers [11–14] and nanoparticles (Fig. 1) [14–18]. In the early 1980s, the classical inorganic cation $\text{Co}(\text{NH}_3)_6^{3+}$ was reported to condense DNA; this cation has advantages over other DNA condensing agents [7,8]. In the first decade of the 21st century, researchers began to study metal complexes to compact DNA and for non-viral gene delivery. The morphologies and sizes of DNA condensates vary depending on the polycation-induced DNA condensate studied and the type of metal complex utilised [19–22]. The mechanistic details of DNA condensation are essential for understanding DNA packing behaviours and guiding its functions or applications. Thus, we have provided an overview of the different types of metal complexes, summarised their DNA condensing mechanisms and shown their applications as gene vectors and as new classes of antitumor agents.

2. Why metal complexes?

Over the last few decades, cationic lipids and polymers have shown significant promise as DNA binding agents, DNA condensing agents and gene vectors in gene therapeutics. Much attention has been focused on the design and synthesis of cationic lipids, polymers and nanomaterials for DNA condensation studies and their applications in non-viral gene vectors [4–18]. However, metal complexes have attracted increasing interest as a novel class of DNA condensing agent [23,24]. The total amount of transition metal elements *in vivo* is less than 0.05%. However, there are many examples in nature that utilise transition metal ions. For example, the zinc finger protein family, consisting of nucleus-targeting molecules, have a nuclear localisation signal within the zinc finger domain, where the zinc can bind tightly [25,26]. Zinc ions have been introduced into polymer–DNA complex systems and increase the gene transfection efficiency because of their ability to associate with the phosphate diester groups that constitute the backbone of DNA [27].

In particular, metal complexes offer some advantages as DNA condensing agents. First, metal complexes exhibit a high positive charge density to neutralise the negative charge of the DNA backbone, which is a prerequisite for DNA condensation. With few exceptions, nearly all lipids or polymers achieve a positive charge through ammonium cations, which provide a +1 positive charge maximum in local sites (not total charges). However, metal ions usually have a +2 positive charge or higher. When coordinated with chelated ligands through rational design, metal complexes

can carry a high positive charge and act as high-density charged nucleation sites for DNA condensation. Second, coordination complexes offer a uniquely modular system for DNA binding. The central metal ion can interact via electrostatic attraction with the DNA phosphate backbone and (or) via base coordination with DNA base pairs. The metal centre can act as an anchor, holding the three-dimensional scaffold of ligands in place, which can also bear DNA-binding elements. Ligands that contain targeting elements can also be easily adopted through metal–ligand coordination. Third, some metal centres benefit from rich photophysical and electrochemical properties, extending their utility far beyond DNA condensing agents and gene vectors. These characteristics have allowed metal complexes to be used in a wide range of applications, such as the luminescent tracking of intracellular gene expression to fabricate smart gene vectors with photo- or electronic-trigger releases.

3. Metal ions

Given the high negative surface charge, the electrostatic repulsion between DNA polyions may be a major force preventing the formation of a compact DNA structures. A sufficient protocol would be to add multivalent cations to neutralise the DNA negative charges. Bloomfield and co-workers [28] have established a simple rule for polycation-induced DNA compaction or aggregation: condensation occurs when ~90% of the DNA charges are neutralised by counterions. Normally, multivalent cations with +3 charges or greater are required for condensing agents in aqueous solution because of charge density effects. The polyamines spermidine³⁺ and spermine⁴⁺ and the inorganic cation $\text{Co}(\text{NH}_3)_6^{3+}$ are most commonly used to effectively condense DNA at micromolar concentrations.

Metal ions can interact with the major and minor grooves of DNA through electrostatic attraction or coordination with DNA base pairs, and may play key roles in the control of the DNA conformation and topology [28–31]. Monovalent cations, such as Na^+ or K^+ , cannot induce DNA condensation unless an additional osmotic pressure is exerted by neutral polymers, such as polyethylene glycol (PEG), which is called a ψ -DNA or psi-DNA compact (“polymer-and salt-induced” DNA condensation) [32,33]. Thus, the forces pushing the double helices together are coming from entropic random collisions with the crowding polymers surrounding the DNA, and monovalent ions are required to neutralise the DNA charges and decrease the DNA–DNA repulsion.

Divalent cations, even at molar concentrations, cannot condense double-stranded DNA (dsDNA) from dilute solutions, except under special conditions if the DNA is circular [20] or in a water–alcohol mixture [34]. However, the effects of divalent metal ions, including Cu^{2+} , Zn^{2+} , Mn^{2+} , Ca^{2+} and Mg^{2+} , on the DNA structural transition have been investigated, and the results indicated that DNA assumed a compact form upon interaction with divalent metal ions,

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